

Preface

In animals and plants, development is controlled by the orchestrated interaction of gene networks responsible for shaping cell differentiation and morphogenesis. The identification of major families of developmental genes in the 1980s and 1990s started shedding light on the components of signalling pathways and their interplay with transcription factors to impose specific developmental programs. The plethora of phenotypes generated by transgenics technology in various organisms helped to decipher several levels of complexity and suggested that gene function might be intimately linked to chromatin accessibility and alteration at key developmental loci. Over the last decade, an explosion of data from the genome-wide exploration of regulatory regions has indicated that epigenetic modifications of chromatin structure play an essential role in the regulation of gene expression. It is now conceivable that developmental strategies largely rely on epigenetic mechanisms to establish and stabilize appropriate gene expression patterns. While cell differentiation uses a genetic program to generate a specific profile of gene activity, the setting of these expression patterns involves genome-encoded mechanisms which functionally mark genomic loci. In a differentiating cell, a selected group of genes functions in a highly tuned manner, while large parts of the genome remain silent. During this process called “reprogramming”, a differentiating cell is set to execute a program, which can be considered as epigenetic since it governs the function of the genome in a heritable manner without affecting the DNA sequence. Here the real epigenetic world starts, since the establishment and maintenance of epigenetic marks is reversible and heritable and responds to a large spectrum of external stimuli.

Our knowledge of epigenetics is still rather elementary. Major issues dealing with the basic features and functionalities of epigenetic developmental control remain to be explored:

- i) What is the nature of epigenetic information?
- ii) How are epigenetic marks established and maintained?
- iii) How are they interpreted?
- iv) What is the epigenetic state of embryonic and adult stem cells?
- v) What is the implication of nuclear architecture and nuclear compartmentalization for the establishment of long-range chromosomal contacts affecting epigenetic control?
- vi) Do non-coding RNAs play a role in epigenetic developmental regulation?

Our aim in this Special Issue of *The International Journal of Developmental Biology* was to summarize current knowledge on these questions and to discuss it in the context of developmental events in animals and plants.

Multiple supports for epigenetic information

An absolute criterion for an epigenetic phenomenon is that it is heritable, although not directly encoded by DNA. The major question raised by this definition concerns the nature of the molecules capable of storing information and passing it over generations. The cleverest way to achieve this mission without using the genetic code would be to load information onto DNA itself, or onto DNA packaging elements such as histones. There are two direct advantages in using DNA and DNA-associated proteins as a support for heritable non-genetic information. First, they can directly affect the organization and hence the function of the genome in a loci-specific manner (contributions from Feil; Sasai and Defossez; Ikegami *et al.*) and second, since this support is present in mature germinal cells, the associated information can be directly transmitted to the offspring (contributions from Feil; Ikegami *et al.*). Accordingly, researchers have rapidly identified meaningful chemical modifications first of DNA then of histones (Sasai and Defossez; Ikegami *et al.*) and started to decipher their functional significance. Additionally, the very nature of DNA-packaging proteins, such as specific histone variants associated with particular genomic regions, also contributes to the regional differentiation of the genome and hence potentially carries epigenetic information (contributions by Godde and Ura; Orsi *et al.*). The very hot questions are now whether other molecules and cellular components, apparently unrelated to DNA or nucleosomes, are also used to convey epigenetic information and how their associated information is transmitted. Very recent investigations point to RNA as another essential component of a carrier system conveying epigenetic information over generations (see contributions by Verdel *et al.*; Eymery *et al.*).

Writers, erasers and readers of epigenetic information

The packaging of DNA, similar to any type of packaging in ordinary life, needs the establishment of a specific tagging system to indicate where everything is packed. An elementary function of epigenetic marks could therefore be the indexation and tagging of genomic information. Specific states of a single gene or that of large domains of the genome could be indicated by a combination of marks, which could also be considered as elements of regional differentiation of the genome. Specific chemical modifications of DNA and histones in the endless repetitions of canonical nucleosomes allow the introduction of regional differentiation and hence bear information regarding the potential of the packaged genes in terms of activity. Epigenomic profiling of regulatory regions suggests that recruitment of histone modifying enzymes is targeted to control specific developmental scenarios such as embryonic stem cell pluripotency, homeotic gene regulation and nuclear hormone receptor activated pathways. The occupancy of enhancer-associated receptor response elements results in local histone modifications which could define antagonizing activities and specific types of heritable chromatin.

These epigenetic marks are established and erased by dedicated enzymatic machineries with tightly regulated functions. It is now clear that these enzymes are the endpoint of complex signalling systems allowing rapid modifications of epigenetic marks as a function of external stimuli (see contributions by Brunmeir *et al.*; Martin *et al.*; Vaquero; Hublitz *et al.*; Vidal; Avramova). They create therefore a real interface between the genome and its environment and explain why the immediate surrounding of a cell or an organism can stably and heritably affect its pattern of gene expression.

The functional interpretation of epigenetic marks requires the existence of molecular mechanisms capable of reading and translating the embedded information. Indeed, an important leap in our understanding of epigenetics occurred after the discovery of cellular factors capable of recognizing and binding to specific chemical modifications of histones and DNA. In fact, besides the probable direct structural modifications due to histone marks, these readers of epigenetic modifications ensure appropriate functional alterations of the genome, in the regions marked with a specific code (see contributions by Feil; Sasai and Defossez; Ikegami *et al.*; Hublitz *et al.*; Vidal).

Inheritance of epigenetic information and the expression of complex traits

Sexual reproduction requires specialized germ cells and establishment of reproductive organs in developing organisms (see contributions by Western; Massé *et al.*). While the female gametes preserve their genome in an almost somatic type configuration, the male gametes, because of the necessity to leave the organism where they were produced and to confront the external environment, undergo a most dramatic structural reorganisation, including an extreme genome compaction. This specific process is conceptually related to the genome compaction which occurs during sporulation in lower eukaryotes (see contribution by Govin and Berger). Due to these spectacular genomic reorganizations, most of the histone associated epigenetic marks are non-existent in the mature male gamete, while they are present in oocyte chromatin and transmittable to the embryo. Therefore, the two parental genomes present an asymmetry which is maintained in the zygote, and whose functional significance remains to be elucidated. During later development, differential epigenetic marks directly inherited from parental genomes, continue to distinguish sets of genes according to their maternal or paternal origin and direct their mono-allelic expression (see paper by Feil).

Epigenetic control of gene expression not only maintains expression of differentiated phenotypes, but could also be involved in complex and sudden modifications of gene expression on the scale of a whole organism, in response to environmental signals. Mammalian hibernation is a survival strategy, which perfectly exemplifies a large-scale gene response to an external change, which may largely rely on the interplay between cell metabolism and epigenetic modulators to modify gene expression (see contribution by Morin and Storey).

Finally, we would like to express our warmest appreciation and gratitude to the Editor-in-Chief and Editorial Team of *The International Journal of Developmental Biology* for providing us with this unique and timely opportunity to present a window on Epigenetics today. Enjoy the read!

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